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CLINICAL UPDATE

Hepatitis C and HIV Infections: Implications for Clinical Care in Injection Drug Users

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Our objective is to provide a state-of-the-art review on hepatitis C (HCV) and the human immunodeficiency virus (HIV) in injection drug users (IDUs), highlighting important clinical issues. We performed a literature review from the MEDLINE database for research from 1966 to 2003, with an emphasis on recent consensus documents. Of the estimated 15 million illicit drug users in the U.S., approximately 1.0 to 1.5 million inject drugs. IDUs are at significant risk of contracting HCV and HIV, with IDUs accounting for 60% of new HCV cases and 25% of new HIV infections. It is a major risk factor for HCV/HIV coinfection, which significantly impacts on each disorder's progression. It appears that treatment response in IDUs with HCV or HIV is similar to non-IDUs with these viruses and that medication adherence and treatment outcomes are optimized when linked with substance abuse treatment. Providers caring for patients who are or were IDUs must be aware of the management of these diseases and make efforts to integrate their medical care with the treatment of their substance abuse. (Am J Addict 2004;13:1–20)

There is a well-documented association between injection drug use (IDU) and both hepatitis C (HCV) and the human immunodeficiency virus (HIV). The number of injection drug users infected with these viruses presents a major public health concern in terms of viral transmission to others and exposes the infected individual to the risks of complications from chronic liver disease and the acquired immunodeficiency syndrome (AIDS). Given the high prevalence of infection with these

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viruses in the IDU population, clinicians caring for these patients should be educated on which tests to order and how to interpret the results, the appropriate management and treatment strategies, and the recommended screening and vaccination practices.

METHODS

Literature for this review came from English-language articles identified through the MEDLINE database (1966 through June 2003) using the following key words: *hepatitis C, HIV, human immunodeficiency virus, AIDS, and injection drug user*. Consensus statements, conference proceedings, and systematic review articles were searched for relevant material. The bibliographies of relevant studies were also reviewed.

HEPATITIS C

Epidemiology

HCV, established as the major cause of non-A, non-B hepatitis in 1989,[1] infects 170 million people worldwide.[2] It is the most common chronic blood-borne infection in the U.S., affecting an estimated 1.8% of the population.[3] The number of new cases per year decreased by 85% from the 1980s to 1996, due to a 50% reduction in transfusion-associated cases and the institution of HIV-prevention programs for IDUs.[3–7] Of the 3.9 million people in the U.S. who are antibody-positive, 2.7 million are chronically infected with a detectable ribonucleic acid (RNA).[5,7,8] Forty percent of chronic liver disease is HCV-related,[3] making it the most common cause of chronic liver disease and the primary reason for liver transplantations performed in the U.S. Eight thousand to ten thousand deaths are attributed to HCV annually.[9]

Risk factors for HCV include IDU, intranasal drug use, hemodialysis, high-risk sexual behaviors, health care exposures, blood product transfusions, and receipt of HCV-infected transplanted organs.[6,10] No identifiable risk factor for HCV is found in 10% of patients.[3]

Despite a significant reduction of HCV cases in IDUs since 1989,[3] IDU is still the major risk factor for transmission in the U.S., accounting for 60% of new cases[3,4] and 20–50% of chronic infections. Approximately 80% of IDUs will develop HCV antibodies after one year of drug use.[11] Half of the patients with HCV deny previous IDU, although recent data revealed illicit drug use in greater than 80% of these patients.[7]

Diagnostic Strategies and Clinical Course

Laboratory Diagnosis. Clinicians who suspect HCV should obtain alanine transaminase (ALT), aspartate aminotransferase (AST), total protein, albumin, and prothrombin time to evaluate hepatic status, and enzyme immunoassay (EIA) to determine antibody status. While the most common laboratory finding is an elevated ALT, it is normal in 30–40% of patients with chronic HCV.[3] Both the EIA and the recombinant immunoblot assay (RIBA) detect HCV IgG with a sensitivity and a specificity of greater than 95%.[10,12]

Reverse transcriptase polymerase chain reaction (RT-PCR)-based assays can detect the presence of HCV RNA within one to two weeks of exposure, while the less sensitive quantitative tests measure the viral burden in RNA/ml.[3] With the high incidence of hepatocellular carcinoma (HCC) in patients with cirrhosis, some recommend that screening serum alpha-fetoprotein (AFP) levels and liver ultrasonography should be performed every six to twelve months.[13,14] However, a recent systematic review examining the utility of AFP levels for detecting HCC in patients with HCV concluded that AFP

has significant limitations in its ability to detect HCC in this population.[15] In addition, for unclear reasons, elevated AFP levels have also been found in patients with chronic HCV without HCC; therefore these results must be interpreted carefully.[16]

Acute HCV Infection. While acute HCV is rarely diagnosed because most patients are asymptomatic, symptoms of acute infection include malaise, nausea, right upper quadrant pain, and jaundice.[17] The average time from exposure to symptoms is approximately six weeks,[18] while that from exposure to antibody seroconversion is approximately eight weeks. Of patients with acute HCV, 75–85% will become chronically infected.[3]

Chronic HCV Infection. Fatigue is the most common presenting complaint of patients with chronic HCV. Other complaints include nausea, anorexia, myalgias, and arthralgias. There are numerous extrahepatic manifestations of HCV, with cryoglobulins detected in approximately one-third of patients, but only 1–2% of patients have clinically significant cryoglobulinemia (see Table 1).[17,19] Disease progression typically follows an indolent course, with the time from exposure to chronic liver disease often being decades.[20] One study revealed that alcohol intake exceeding 50g/d, advanced age, and male gender accelerated disease progression.[21] Cirrhosis develops in 20% of patients with chronic HCV within 20 years from the time of exposure;[22] HCC develops in one to five percent of patients with chronic HCV and one to four percent of patients per year with cirrhosis.[3]

Management/Treatment

Lifestyle modifications. Patients with HCV should avoid alcohol, hepatotoxic medications, high-risk sexual practices, and IDU. These practices increase the risk for contracting HBV or HIV, and coinfection with these viruses significantly affects progression of HCV. While approximately 15–20% of patients with acute HCV have a history of sexual contact with a known infected person or multiple sexual partners,[3,9] patients' spouses without other HCV risk factors have an infection rate of up to 4.4%.[3] Therefore, the Centers for Disease Control and Prevention do not recommend changing sexual practices in HCV-infected individuals engaged in long-term relationships but suggest considering the use of barrier precautions and pursuing counseling and testing.[3]

Postexposure prophylaxis. While there are data for the efficacy of postexposure prophylaxis (PEP) in HBV and HIV,[23] there are currently no clinical trials that have examined PEP for HCV.

Pretreatment management. Previously, alfa-interferon (IFN) monotherapy or IFN in combination with ribavirin were the mainstays of treatment for HCV infection. The attachment of polyethylene glycol to IFN created pegylated IFN peginterferon, which is now routinely used in combination with ribavirin. Success of treatment is measured by the sustained virological response (SVR), which is defined as the absence of detectable RNA at the end of treatment and 24 weeks posttreatment. However, prior to initiation of treatment of HCV, certain pretreatment variables in patients must be obtained and evaluated.

HCV genotype has an impact on response to therapy. There are at least six different genotypes and greater than ninety subtypes,[24] with 70% of HCV-infected patients in the U.S. having genotype 1 and the remainder with genotypes 2, 3, and 4.[25] Type 1 has a less favorable prognosis and response to treatment. A recent randomized trial[26] comparing the addition of ribavirin

TABLE 1. **Extrahepatic Manifestations of HCV Infection**[17,19]

Cryoglobulinemia
Membranoproliferative glomerulonephritis
Porphyria cutanea tarda
Sjogren's syndrome
Seronegative arthritis
Lichen planus
Idiopathic pulmonary fibrosis
Non-Hodgkin's lymphoma
Polyarteritis nodosa
Aplastic anemia
Autoimmune thyroiditis

to a higher dose peginterferon or to IFN found that the benefit of peginterferon varied by genotype subgroups. A higher SVR with the peginterferon combination was seen in genotype 1 (145/348, 42% vs 114/343, 33%, $p = 0.02$) when compared with the IFN combination, while no difference was seen in genotype 2 and 3 (121/147, 82% vs 114/146, 79%, $p = 0.46$). In turn, the higher dose peginterferon/ribavirin combination produced an SVR of only 42% in the subgroup with genotype 1, as opposed to an SVR of 82% in genotypes 2 and 3.

Pretreatment RNA levels, although not predictive of disease progression,[27,28] appear to predict response to IFN-based regimens. Patients with RNA > 2 million copies/ml are less likely to respond to therapy.

Indications for treatment include patients ages 18 to 65 years, persistently detectable RNA and elevated ALT levels (> 6 months), and moderate inflammation, fibrosis, or necrosis on biopsy. A liver biopsy is the gold standard for staging disease, prior to initiating treatment[17] or for patients who fail to respond to treatment.[29] Patients with an elevated ALT but minimal changes on biopsy may receive treatment or have serial liver function tests performed and a biopsy repeated in three to five years.[17,30] Biopsies in patients with normal ALTs are controversial but should be considered given that ALT levels correlate poorly with histopathological findings.[17] One study revealed that 20% of patients with repeatedly normal ALT levels had advanced liver disease.[31]

Treatment of acute HCV infection. Acute HCV is rarely diagnosed, and there is little consensus on when and how to start treatment. A recent study found that 42 of 43 (98%) patients with acute HCV who received 24 weeks of IFN treatment had undetectable RNA levels and ALT normalization at four and 24 weeks.[32] Early treatment aborted progression to chronic infection, and response to treatment was not affected by genotype or mode of transmission.

Treatment of chronic HCV infection. Monotherapy with IFN carries a 40% initial response rate (undetectable HCV RNA) and a 20% SVR.[27,28] Greater than 90% of patients treated with IFN who have normal ALT levels and undetectable RNA six months after therapy will have sustained viral suppression and histological improvement.[33] A trial comparing IFN alone or with the addition of ribavirin found the rate of SVR to be higher in the combination regimen at 24 weeks (70/228, 31%) than with the IFN alone group at either 24 (13/231, 6%) or 48 (29/225, 13%) weeks ($p < 0.001$). Similarly, there was a higher rate of histological improvement in the

combination regimen at 24 (102/179, 57%) weeks than in the IFN group at 24 (77/176, 44%) or 48 (65/158, 41%) weeks ($p < 0.001$).[27,28]

Modified IFN, peginterferon, produces a greater response rate and makes weekly administration possible.[34,35] In one study, peginterferon increased the SVR rate as compared to the unmodified IFN at both week 48 (185/267, 69% vs 73/264, 28%, $p = 0.001$) and week 72 (103/267, 39% vs 50/264, 19%, $p = 0.001$).[35] In addition, the positive effects of peginterferon were seen in patients with genotype 1 who had previously been unresponsive to treatment. In a previously mentioned recent randomized trial[26] comparing higher dose peginterferon/ribavirin versus IFN/ribavirin, researchers found a greater SVR in the higher dose peginterferon/ribavirin combination (275/511, 54%) than in the IFN/ribavirin (244/514, 47%, $p = 0.01$) at a 72-week follow-up in all patients.

Once treatment has been initiated, current recommendations include monitoring patients regularly, assessing for symptoms and checking blood counts and liver function tests. After 24 weeks, HCV RNA should be checked. Patients with genotype 2 or 3 and an undetectable RNA should discontinue therapy, and RNA and ALT should be checked six months after treatment. Patients with genotype 1 and an undetectable RNA at 24 weeks should continue treatment for an additional 24 weeks. Patients with a detectable RNA at 24 weeks of treatment should discontinue treatment and be considered for enrollment in clinical trials.[17]

Patients with decompensated cirrhosis or early HCC should not be treated with currently available therapy but be evaluated for liver transplantation despite the evidence that nearly 100% of patients will have reinfection of the graft.[36–38]

Side effects. IFN can cause fatigue, headache, fever, and myalgias.[39,40] Other side effects include bone marrow suppression with pancytopenia, and depression is particularly treatment-limiting. Neuropsychiatric effects from IFN are more common in individuals with a history of psychiatric disorders.[28,41,42] They develop in 10–40% of patients and may be severe enough to lead to discontinuation of treatment in 5–15%.[3] There are reports of IFN leading to both suicidal ideation and suicide.[43] Given the high rate of psychiatric comorbidity in IDUs,[44] providers must monitor for these side effects and consider the addition of an antidepressant prior to treatment to help control depressive symptoms.[45] The most significant side effect of ribavirin is a hemolytic anemia, which can necessitate a dose reduction.[28]

Treatment of HCV infection in IDU. There have been recommendations[17,46,47] to withhold HCV treatment from active injection drug users, advocating the treatment of the drug misuse before commencing antiviral therapy, with the rationale that drug use poses a greater immediate threat than untreated HCV. Another rationale for withholding therapy in these active users is that with treatment they may clear the virus, only to be re-infected with ongoing IDU. Withholding HCV treatment from IDUs raises ethical and public health concerns. One way to control HCV infection is to treat IDUs. The 1997 NIH guidelines for the treatment of HCV recommended six months of abstinence prior to starting treatment, given that IFN can be associated with relapse in individuals with a substance use disorder.[48] There is evidence that individuals with HCV and concurrent substance abuse have lower SVR rates than patients with HCV who are not abusing illicit drugs;[41,42,49,50] though this finding is thought to be secondary to decreased adherence and suppressed cellular immunity. In addition, the majority of IDUs with HCV lack knowledge about disease transmission and their serostatus, with

67% of seropositive patients in one study reporting they were HCV seronegative. Despite this finding, greater than 50% of IDUs were willing to receive HCV treatment.[51,52]

Several recent studies have examined the treatment of HCV in IDUs undergoing treatment for opioid dependence. In one study, 36% of the fifty patients undergoing methadone detoxification had an SVR, and while many patients suffered a relapse, there were no cases of reinfection during the 24 weeks after treatment.[53] Another study of methadone-maintained patients receiving HCV treatment revealed that 78% of the fifty patients completed treatment with a virologic response rate of 64%.[54] While the data from these studies support the hypothesis that IDUs with chronic HCV infection can be treated successfully for their viral infection within the context of treatment for their substance use disorder, given that active IDUs have been excluded from clinical trials of HCV treatment, the data in active drug users is scarce.

The section of the new NIH 2002 guidelines focusing on the treatment of HCV in drug users reflects some optimism. New guidelines promote collaboration between HCV experts and addiction specialists, with a statement that HCV treatment of active IDUs should be considered on a case-by-case basis, and more importantly, that they should not be excluded from treatment.[55] It has been suggested that in addition to addressing their patient's substance use disorder, clinicians should thoroughly evaluate the mental health of their IDU patients, improve adherence strategies, advocate safe injection practices, and optimize the timing of treatment so that active injection drug users benefit from the available therapies.[56]

The effects of opioid agonist treatments on HCV. It is important to consider the effects of opioid agonist treatment on liver function in patients with HCV. An early study[57] of methadone maintenance (80–120 mg/day) in patients with or without preexisting liver disease found no evidence of hepatotoxicity in the 129 patients who were maintained in treatment for three or more years. A second study[58] of 116 IDUs with HCV infection receiving methadone, naltrexone, or a drug-free regimen found elevated transaminases only in the drug-free group. A further study that looked at the effects of methadone on a cellular level found that therapeutic doses of methadone were unlikely to produce irreversible hepatocyte damage, with higher than therapeutic doses causing liver dysfunction.[59] Other studies examining methadone maintenance in patients with chronic liver disease found that methadone doses could be safely continued in patients with stable liver disease.[60,61]

Of note, the side effects of IFN can have a significant impact on the treatment of patients with HCV and IDU in that they can mimic the symptoms of opioid withdrawal; therefore, providers need to conservatively manage these side effects. Despite these issues, methadone maintenance therapy is not contraindicated in patients with HCV infection, and those with both HCV and opioid dependence can be successfully treated.[54]

Buprenorphine, a partial mu opioid agonist recently approved by the Food and Drug Administration for the treatment of opioid dependence, is not known to have significant hepatic effects when administered via the sublingual route. Early studies found buprenorphine to be well tolerated, and while some patients developed elevated transaminases, this finding could not definitively be ascribed to the medication.[62] A study[63] examining buprenorphine's effects on liver function found elevated liver enzymes in the 72 out of 120 patients with underlying hepatitis receiving

sublingual buprenorphine. While the median increases in ALT (8.5) and AST (9.5) were minimal, they were statistically significant. Symptomatic hepatitis developed in only three patients, and the transaminase increases appeared to be dependent upon the buprenorphine dose. The investigators concluded that the monitoring of liver enzymes is indicated in the setting of HCV infection and buprenorphine treatment. One series of four case reports[64] found increases in transaminases thirty to fifty times that of normal with the intravenous administration of buprenorphine in patients infected with HCV. Of note, this study reported only a small number of cases, and the subsequent hepatitis was thought to be directly related to the higher concentrations of buprenorphine delivered by injection and thus thought to not occur with sublingual administration. Generally, it is recommended that baseline and periodic measurements of liver function tests be performed when a patient with HCV is initiated on buprenorphine.

HIV/AIDS

Epidemiology

HIV, first reported in the early 1980s, is a blood-borne infection that causes a progressive depletion in CD4+ lymphocytes. This marked reduction leads to profound immunosuppression, with the development of the opportunistic infections and neoplasms that constitute AIDS. Globally there are 36.1 million people living with HIV/AIDS.[65] At the end of 2000, 775,000 persons are reported to have had AIDS in the U.S.[66] There are approximately 40,000 new infections each year, with 60% of men infected through homosexual sex, 15% through heterosexual sex, and 25% through IDU. In women, 75% are infected via heterosexual sex and 25% via IDU.[67]

The number of IDUs living with AIDS has significantly increased from 48,244 in 1993 to 88,540 in 1999.[66] The increasing prevalence of IDUs living with AIDS may indicate that with better pharmacological treatment, these individuals are living longer.[68]

Diagnostic Strategies and Clinical Course

Laboratory diagnosis. Enzyme-linked immunosorbent assays (ELISAs) detecting IgG to HIV-1 should be the first screening test performed. A reactive ELISA needs confirmation with the more specific Western blot (see Table 2).[69,70]

Assays that detect HIV include nucleic acid detection of HIV RNA (viral load), p24 antigen, and HIV culture. Detection and quantification of HIV RNA are used to evaluate for acute infection and determine the need for and assess response to antiretroviral treatment.

Acute HIV Infection. Forty to ninety percent of patients with acute HIV infection or acute retroviral syndrome exhibit symptoms.[71] The time from exposure to

TABLE 2. **HIV Viral Markers[69,70]**

Viral Marker	Appearance after Infection	Sensitivity (%)	Specificity (%)
Routine serology with ELISA	20–21 days	100	99
Plasma RNA	11 days	90–95	97
P24 antigen	14–15 days	8-32	100

ELISA = enzyme-linked immunosorbent assay
RNA = ribonucleic acid.

onset of symptoms is typically two to six weeks, with the acute illness lasting one to two weeks.[72] Patients typically describe a flu-like syndrome with fever, fatigue, and pharyngitis.[71,73,74]

The most sensitive test for diagnosing acute infection is RNA. Patients with a negative or indeterminate antibody but detectable RNA are considered to have acute infection. The assay, however, has a false positive rate of 1.9% to 3%.[75] Because RNA levels are generally greater than 100,000 copies/ml in acute infection, clinicians should question the diagnosis in patients with significantly lower levels.[76]

Greater than 95% of people seroconvert in less than six months. In patients who test seronegative, antibodies should be repeated within three to six months if infection is suspected.[71] Other laboratory findings consistent with acute infection include a transient pancytopenia.[72]

The clinical features of acute infection, including the baseline mean CD4 count and viral load, are similar in patients who are infected sexually or via IDU.[77] One study, however, of HIV-infected IDUs found that HIV infection was associated with a more rapid decline in CD4 counts and progression to AIDS.[78]

Chronic HIV Infection. The rate of progression to AIDS is variable and dependent on factors such as the use of opportunistic infection prophylaxis and antiretroviral therapy.[68,79] Without treatment, the median time from initial infection to AIDS is eight to ten years.[80] The viral load predicts the rate of CD4 count decline and progression to AIDS and death. The viral load, in combination with CD4 count, best assesses prognosis.[81]

The predictive value of the viral load does not vary between high-risk groups such as IDU or homosexual men.[81,82] While earlier studies suggested that there was a more rapid decline in IDUs, more recent research has shown no significant differences in baseline or longitudinal viral load measurements or in the rate of development of AIDS in IDU vs non-IDU populations.[83–86] In contrast, age and gender appear to have a significant effect on disease progression. The risk of developing AIDS significantly increases with age, a finding seen across different exposure groups.[85,86] Similarly, women have a similar rate of disease progression as men despite a lower initial RNA level.[87,88]

Finally, approximately five percent of individuals are considered to be long-term nonprogressors, remaining healthy and immunologically intact for greater than a decade from seroconversion.[89] These individuals have a low viral burden, strong virus-specific immune responses, and moderate viral attenuation.[90] Certain demographic findings, such as a history of IDU, age, or gender, did not differ in individuals with or without non-progressive HIV infection.[91]

Management/Treatment

Lifestyle Modifications. Prevention must be targeted at HIV-infected individuals in order to slow the spread of infection. The key risk behaviors for transmission are nonsterile IDU, unprotected anal and vaginal intercourse, and intercourse with multiple partners.[92] Several agencies released recommendations for health professionals on how to advise their patients who continue to inject drugs (see Table 3).[93]

A recent study showed that in a high-seroprevalence population of IDUs, the HIV incidence rate was low compared to previous years.[94] A subsequent study documented reductions in risk behaviors with expansion of syringe exchange programs and HIV counseling and testing.[95] Despite the decline in new AIDS

TABLE 3. **Recommendations for Persons Who Continue to Inject Illicit Drugs**

Stop using and injecting drugs
Enter and complete substance-abuse treatment, including relapse prevention
Never reuse or "share" syringes, water, or drug-preparation equipment
Use only syringes obtained from a safe, reliable source (eg, pharmacies)
Use a new, sterile syringe to prepare and inject drugs
If possible, use sterile water to prepare drugs; otherwise use clean water from a reliable source (such as fresh tap water)
Use a new or disinfected container ("cooker") and a new filter ("cotton") to prepare drugs
Clean the injection site before injection with a new alcohol swab
Safely dispose of syringes after each use

Recommendations are from consensus of the Centers for Disease Control and Prevention, the National Institute on Drug Abuse, the Health Resources and Services Administration, and the Substance Abuse and Mental Health Services Administration[92]

cases in injection drug users, which can be attributed both to prevention programs and potent antiretroviral therapy, one of the objectives of the Healthy People 2010 campaign is to decrease the incidence by 25%.[96] An additional goal is to increase the proportion of substance abuse treatment facilities providing HIV/AIDS counseling, given that providing substance abuse treatment has been demonstrated to be the best way to prevent HIV transmission associated with drug use.[96]

Postexposure Prophylaxis. While the U.S. Public Health Service does not definitively recommend nonoccupational HIV postexposure prophylaxis, other groups have recommended it.[97] With the IDU population, there is concern that postexposure prophylaxis will be viewed as a safety net allowing continued high-risk behaviors or even a shift from lower to higher risk activities with the perception that postexposure prophylaxis prevents HIV infection. Other concerns include cost, adherence, development of drug resistance, and known medication toxicity.[97–99] Continued drug use increases the likelihood of repeated exposure, medication non-adherence, and drug resistance, making the administration of postexposure prophylaxis more challenging. Nonetheless, a recent study demonstrated that the majority of providers felt that an injection drug user with a high-risk nonoccupational exposure should be offered postexposure prophylaxis. It has been proposed that postexposure prophylaxis might be most successful in users enrolled in drug treatment programs.[100]

Pretreatment Management. HIV RNA and the CD4 count provide prognostic information in both IDU and non-IDU patients with HIV.[101] Patients with the lowest baseline CD4 count and the highest RNA level receiving antiretroviral therapy had the highest risk for disease progression or death.[102] In a separate study, a low baseline RNA level predicted a more favorable virological response with antiretroviral therapy.[103] In contrast, a recent study showed that lower baseline CD4 counts and higher RNA levels were not associated with a worse virological outcome with antiretroviral therapy, but that patients with baseline RNA levels of greater than 100,000 copies/ml had a slower rate of viral suppression.[104] Finally, another study found that the CD4 count prior to the initiation of therapy was the only independent prognostic indicator, with progression to AIDS or death clustered

TABLE 4. **Indications for the Initiation of Antiretroviral Therapy in the Chronically HIV-1 Infected Patient**

Clinical Condition	CD4+ Lymphocyte Count	HIV RNA	Treatment Recommendations
Symptomatic, AIDS	Any value	Any value	Treat
Asymptomatic, AIDS	CD4+ $< 200/mm^3$	Any value	Treat
Asymptomatic	CD4+ > 200 m^3 but $\leq 350/mm^3$	Any value	Offer treatment, but controversial
Asymptomatic	CD4+ $> 350/mm^3$	$> 55{,}000$ (RT-PCR or bDNA)	Consider recommending therapy. Three-year risk of developing AIDS in untreated patients is $> 30\%$; in the absence of increased viral RNA, the physician could defer treatment and monitor CD4+ counts and RNA more frequently
Asymptomatic	CD4+ $> 350/mm^3$	$< 55{,}000$ (RT-PCR or bDNA)	Consider deferring therapy. Three-year risk of developing AIDS in untreated patients is $< 15\%$

CD4+ lymphocyte = the CD4 subset of T-helper lymphocytes
bDNA = proviral deoxyribonucleic acid
RT-PCR = reverse transcriptase as determined by polymerase chain reaction.
These indications are adapted from the Department of Health and Human Services Guidelines.[160]

around patients with CD4 counts of less than 200×10^6/L.[105] This study also revealed that the RNA level was not independently associated with survival. There is also evidence that the rate of increase in viral load over time is highly predictive of the development of AIDS.[83]

Treatment of Acute HIV Infection. Data indicate that treatment during early infection produces a vigorous HIV-specific response of CD4 lymphocytes and undetectable RNA.[106,107] A recent study showed that patients receiving antiretroviral therapy during acute infection had fewer opportunistic infections and reduced progression to AIDS.[108] Acute infection is one of the indications for offering treatment.[71,74]

Treatment of Chronic HIV Infection. Highly active antiretroviral therapy (HAART) consists of two nucleoside reverse transcriptase inhibitors (NRTI) combined with either a third NRTI, a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI).[74] The first nucleotide reverse transcriptase inhibitor, tenofovir or Viread, was recently approved for use in the treatment of HIV. In addition, enfuvirtide (T20, Fuzeon) is a novel agent, recently approved for the treatment of HIV, that binds and selectively inhibits fusion of the HIV virus to the CD4 cell.[109]

HAART has had a profound impact on the morbidity and mortality associated with HIV and AIDS.[68,110] One study revealed decreased mortality in patients treated with HAART from 29.4 per 100

TABLE 5. **Recommended Vaccinations in HCV and/or HIV Infections**[138–141,142–146]

Vaccination	Indicated in HCV	Indicated in HIV
Streptococcus pneumoniae: Pneumovax 0.5 ml IM×1, at 3–5 year intervals	X	X
Influenza: 0.5 ml IM, yearly	X	X
Hepatitis B series: Recombivax HB 10 μg IM×3 or Energix-B 20 μg IM×3 at zero, one, and six months	X	X
Hepatitis A series: Havrix 0.5 ml IM×2, separated by six months	X	X
*Combined hepatitis A/hepatitis B series: Twinrix 1 ml IM of 720 ELISA units inactivated hepatitis A viral antigen and 20 μg recombinant HbsAg protein ×3 at zero, one, and six months.	X	X
Tetanus	X	X
Haemophilus influenzae B		X

*In substitution for the single antigen hepatitis vaccines.

person-years in 1995 to 8.8 per 100 by 1997.[68] Similarly, the incidence of AIDS-defining illnesses decreased from 50 per 100 person-years before HAART to 13.3 after HAART. While the timing to initiate antiretroviral therapy remains controversial, Table 4 outlines the most recent recommendations.[74]

Prior to initiating therapy, clinicians and patients must discuss medication adherence, side effects, and safe sex and injection drug-related practices.[74] One study revealed that with adherence of 95% or greater, there were no opportunistic infection events or deaths.[111] In addition, adherence helps to prevent the incomplete suppression of viral replication leading to resistance mutations.

The goals of HAART include long-standing viral suppression, restoration and preservation of immunological function, improved quality of life, and decreased HIV-related morbidity and mortality. The RNA level gauges the success of therapy with the expectation of a one-$\log_{10}$ decrease at eight weeks and an undetectable viral load (< 50 copies/ml) at four to six months following initiation of treatment.[74]

Given the concern for drug resistance, an important adjunct to treatment is the use of (1) genotyping assays that detect mutations in viral genes, and (2) phenotyping assays that measure viral growth in the presence of antiretrovirals.[74] Testing is recommended in the setting of a failing regimen and with multiple regimen failures.[112]

Patients who receive three or more drugs to which their virus is susceptible have the best virological response.[113] One trial[114] found an undetectable RNA in 19/65 (29%) of the genotyped patients vs 6/43 (14%) in the control group ($p = 0.017$) at three months. Similarly, at six months, an undetectable RNA was found in 21/65 (32%) of the genotyped patients vs 6/43 (14%) in the control group ($p = 0.067$).

The risk for opportunistic infections such as *Pneumocystis carinii, Toxoplasma gondii*, or *Mycobacterium avium complex* increases when the CD4 count declines below 200/mm^3, 100/mm^3, and 50/mm^3,

respectively, and primary and secondary prophylaxis should be started accordingly.[115,116] Recent evidence supports the discontinuation of primary and secondary prophylaxis once the CD4 count has remained above a threshold level for greater than three to six months.[115] When the CD4 count declines below that level, prophylaxis should be restarted.

Side Effects. Side effects to HAART therapy include hypersensitivity reactions and mitochondrial toxicity in the form of hepatic steatosis and lactic acidosis with the NRTIs, neuropsychiatric symptoms and hepatitis with the NNRTIs, and osteopenia, hyperlipidemia, and the lipodystrophy syndrome with the PIs.[74,117,118]

Treatment of HIV Infection in IDU. The guidelines for offering antiretroviral therapy should be applied to patients with IDU.[84] While many studies report the efficacy of HAART across risk groups, there are conflicting results. One study comparing adherence and clinical outcome with HAART in IDUs and non-IDUs found that while adherence was greater in the non-IDUs, treatment efficacy was similar in the two groups.[119] In contrast, a study examining disease progression in IDUs vs non-IDUs and in the pre- and post-HAART era, found that the disease-free survival time was extended with the use of HAART but the gains were greater in the non-IDU group.[120]

A recent study found that those with IDU as their HIV risk factor were less likely to receive antiretroviral treatment although over 50% denied recent drug use.[121] In addition, the treating physician's concern about medication compliance in the IDU patient plays a role in those not receiving HAART.[122]

While injection drug users with HIV have high medical comorbidities, they historically have had less access to care. In one study, active users with asymptomatic HIV who had less contact with health care providers were less likely to receive antiretroviral therapy.[123] Even when free antiretroviral therapy was available, many HIV-infected users were not receiving it.[124]

Given that active drug use can decrease medication adherence, substance abuse treatment must be an integral part of HIV management.[125] In a model designed to provide primary care to patients receiving drug treatment, of whom 77% were receiving methadone maintenance, 65% of the 120 patients reported no primary care provider at baseline.[126] Of the 24% of injection drug users with HIV, 89% accepted antiretroviral therapy and 100% accepted *Pneumocystis carinii* pneumonia prophylaxis. After six months, 84% were compliant with antiretroviral therapy and 77% were compliant with prophylaxis, demonstrating the effectiveness of combining HIV care and substance abuse treatment.

The Effects of Opioid Agonist Treatments on HIV. With the integration of substance abuse and HIV treatment, it is crucial to evaluate the potential medication interactions that may occur when simultaneously treating these two conditions. For the NRTI class of medications, methadone was found to increase the area under the curve (AUC) of both intravenous and oral zidovudine (AZT) as well as decrease clearance.[127] In contrast, a second study[128] of NRTIs found that methadone decreased the concentrations of didanosine (DDI) and stavudine (D4T), suggesting that larger doses of these medications may be necessary in patients receiving methadone maintenance. In turn, studies have shown that the NRTI medications did not significantly alter methadone concentrations.[128,129] The NNRTI class of antiretrovirals are potent inducers of the cytochrome P450 enzyme and have been found to significantly decrease methadone

concentrations, requiring increased methadone doses.[130,131] With regards to the PIs, an early in vitro study demonstrated that coadministration of certain PIs with methadone or buprenorphine could result in significantly higher levels of the opioid agonists.[132] In contrast, the findings of a subsequent study revealed a reduction in the AUC of methadone in the presence of PIs but found that this reduction did not lead to opioid withdrawal or require a dose adjustment.[133] Finally, a study looking at the effect of combination therapy with three antiretrovirals (two NRTIs and one PI) found that this triple therapy increased the rate of methadone metabolism, resulting in decreased methadone levels.[134]

A study[135] evaluating the interactions of HIV medications and opioid dependence pharmacotherapies other than methadone compared the effects of LAAM, buprenorphine, and naltrexone on AZT concentrations in 52 subjects and found no significant difference in the AUC for these three treatments compared to controls. Finally, with regard to HIV outcomes in patients receiving buprenorphine for treatment of opioid dependence, a recent study found at a six-month follow-up that there was no major short-term impact of buprenorphine on HIV viral load in patients receiving HAART therapy[136] and that patients receiving buprenorphine as compared to active IDUs, had a significantly higher level of adherence to HAART.[137]

Recommended Vaccinations for IDUs with HCV and/or HIV Infection

Injection drug users with HCV and/or HIV and without serological evidence of immunity to hepatitis A (HAV) or HBV should be vaccinated to prevent superinfection with these viruses.[138] Table 5 outlines the recommended vaccinations for HCV- and HIV-infected patients.[138–146]

THE IMPACT OF HCV/HIV COINFECTION

Approximately 30% of HIV-positive patients in the U.S. are co-infected with HCV.[147] In HIV-infected injection drug users, the prevalence of HCV ranges from 50%–90%.[148,149] The rate of HCV among users is four times greater than that of HIV, illustrating the relative effectiveness of HCV transmission.[11] While sexual transmission of HCV is relatively inefficient in patients with HCV alone, coinfected patients may have an increased risk of acquiring the other virus via sexual contact.[150,151]

HIV has a significant effect on the progression of HCV to severe liver disease.[152–154] After 15 years of infection with HCV, patients coinfected with HIV have a 25% risk of cirrhosis, while those with HCV alone have only a 6.5% risk.[153] There is evidence that HCV coupled with IDU can lead to impaired CD4 cell recovery, increasing the progression of HIV to an AIDS-defining illness or death.[155] Given that HIV-infected patients are surviving longer with HAART, treating HCV in these patients is more compelling, and the potential hepatotoxicity of HAART makes treating HIV in the HCV-infected patient more challenging. Initiating therapy can lead to immune reconstitution, thereby worsening the symptoms of HCV.[156] Coinfection may increase the risk but not the severity of hepatoxicity from HAART, and therefore HAART should not be avoided in these patients; however, transaminases need careful monitoring[146,157,158] and prior treatment of HCV should be considered.[159]

CONCLUSIONS

Injection drug users are exposed to specific and significant risks for HCV and HIV infections via parenteral as well as sexual transmission. They are at risk early in the course of their drug use, and because they

typically do not obtain regular medical care, they usually present in the later stages of disease. In order to improve the medical care of these patients, health care providers need to be aware of these viruses, the appropriate screening, treatment, preventive and referral options, and the intricacies of managing coinfections.

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